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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/516,705	12/02/2004	Takahito Hara	3056 US0P	1003

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EXAMINER	
BRISTOL, LYNN ANNE	
ART UNIT	PAPER NUMBER
1643	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
31 DAYS	01/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/516,705	HARA ET AL.	
	Examiner	Art Unit	
	Lynn Bristol	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-70 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) 1-70 are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-70 are all the pending claims for this application.

2. As "use" claims, claims 17 and 65 are drawn to non-statutory subject matter under 35 U.S.C. §101. Because the claims cannot be reasonably construed as any method, the claims are withdrawn from lack of unity restriction.

Lack of Unity Restriction

3. Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

To have a general inventive concept under PCT rule 13.1, the inventions need to be linked by a special technical feature. The special technical feature recited in claim 1 is an anti-androgen, drug-resistant cancer cell line having a mutant androgen receptor. In view of this the following references teach the same technical feature:

Veldscholte et al. (Biochem. Biophys. Res. Comm. 173:534-540 (12/14/90); cited in the IDS of 12/2/04) teach stimulatory effects of non-androgenic compounds on the growth rate of LNCaP cells having an mutated androgen receptor, and in studies with HeLa cells transfected with the pARL plasmid (mutated AR) and exposed to the anti-androgens, cyproterone acetate and anandron, the cells were activated through the AR;

Hara et al. (Cancer Research 63:149-153 (1/1/03); cited in the IDS of 9/18/06) teach establishing long-term cell lines, LNCaP-FGC, cultured in the presence of the

anti-androgen, bicalutamide, wherein under the selection conditions, the cells were shown to have altered androgen receptor;

Culig et al. (Br. J. Cancer 81(2):242-251 (9/99) teach that LNCaP-abl cells are induced to proliferate with bicalutamide, which otherwise acts as an antagonist on the parental LNCaP cell line. Culig further reports that the non-steroidal AR blocker, hydroxyflutamide, was stimulatory for both the LNCaP-abl and LNCaP cell lines; and

Furr et al. (Urology 47(1A Suppl) 13-25; discussion 29-32 (1/96)) teach that flutamide stimulates the cell line, LNCaP (mutated androgen receptor; codon 868, Thr → Ala) to proliferate.

Therefore the technical feature recited in claim 1 is not special. Accordingly the groups are not so linked as to form a single general concept under PCT Rule 13.1.

4. In accordance with 37 CFR 1.499, applicant is required, in response to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1-4, drawn to a method of making an antiandrogen drug-resistant cancer cell line having the property of proliferating in the presence of the antiandrogen drug and having a mutant androgen receptor.

Group II, claim(s) 5-8, 18 drawn to a cancer cell line having the property of proliferating in the presence of the antiandrogen drug and having a mutant androgen receptor.

Group III, claim(s) 9, 10, 19 drawn to a method of screening for an antiandrogen drug exhibiting antagonist action on an androgen receptor mutant cell line.

Group IV, claim(s) 11, 15, 67 drawn to an antiandrogen drug exhibiting antagonist action on an androgen receptor mutant cell line.

Group V, claim(s) 12 drawn to a method of screening an antiandrogen drug with no potential to induce resistant cancer.

Group VI, claim(s) 13, 14 drawn to an antiandrogen drug having no potential to induce resistant cancer.

Group VII, claim(s) 16 drawn to a method of prophylaxis or treatment for a hormone-sensitive cancer which is androgen dependent or independent using an antiandrogen drug exhibiting antagonist action on an androgen receptor mutant.

Group VIII, claim(s) 20-23 drawn to a kit for evaluating antiandrogen drug responsiveness of androgen receptor transcription activity or screening an androgen receptor modulator, comprising a cell with a gene under a PSA promoter.

Group IX, claim(s) 24-28, 68-70 drawn to a method of evaluating antiandrogen drug responsiveness of androgen receptor transcription activity or screening an androgen receptor modulator.

Group X, claim(s) 29, 30 drawn to an isolated protein of SEQ ID NO:2 and partial peptides thereof.

Group XI, claim(s) 31-41, 59, 61 drawn to a polynucleotide encoding a protein of SEQ ID NO:2, vectors containing the polynucleotide, transfected animal cells, a method for expressing the protein from the animal cell, method for quantitating mRNA using the polynucleotide, method for diagnosing transition from hormone-sensitive cancer to androgen-independent stage.

Group XII, claim(s) 42 drawn to a method of screening a compound that alters the binding of an androgen and a protein of SEQ ID NO:2.

Group XIII, claim(s) 43, 56-58 drawn to a kit for screening a compound that alters the binding between an androgen and the protein of SEQ ID NO:2; compounds that alter binding between an androgen and the protein of SEQ ID NO:2; and pharmaceutical agents thereof.

Group XIV, claim(s) 44, 45 drawn to an agent having anti-androgen action on mutant AR, for prophylaxis or treatment of hormone sensitive cancers.

Group XV, claim(s) 46, 47 drawn to a method of prophylaxis or treatment of hormone sensitive cancers using an agent having anti-androgen action on mutant AR.

Group XVI, claim(s) 48, 49 drawn to a method of making a pharmaceutical composition comprising combining two or more agents having anti-androgen action on different mutant AR with a pharmaceutically acceptable carrier.

Group XVII, claim(s) 50-55 drawn to an antibody recognizing the protein of SEQ ID NO:2.

Group XVIII, claim(s) 60 drawn to a method of quantitating the protein of SEQ ID NO:2 using an antibody that binds the protein.

Group IXX, claim(s) 62 drawn to a method of classifying antiandrogen drugs based on the generation of resistant cancer cell lines that express a different mutant AR from a cell line having a known mutant AR.

Group XX, claim(s) 63 drawn to an agent comprising a combination of two or more antiandrogen drugs, wherein the two or more drugs have been classified on the basis of their ability to generate cell lines each having a different mutant AR.

Group XXI, claim(s) 64 drawn to a method for prophylaxis or treatment of hormone-sensitive cancers using an agent comprising a combination of two or more antiandrogen drugs, wherein the two or more drugs have been classified on the basis of their ability to generate cell lines each having a different mutant AR.

Group XXII, claim(s) 64 drawn to a method for prophylaxis or treatment of androgen-independent, hormone-sensitive cancers, where the cancer has become resistant to one antiandrogen drug, where a second antiandrogen drug classified as inducing expression of a different AR mutation is then administered.

5. The inventions listed as Groups I-XXII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: As set forth above, in view of the teaching of Veldscholte et al., Hara et al., Culig et al. and Furr et al. the groups are not so linked as to form a single general concept under PCT Rule 13.1 because the technical feature of claim 1 is not special.

6. Inventions of Groups II, IV, VI, VII, X, XI, XIII, XIV, XVII and XX represent separate and distinct products which are made by materially different methods, and are used in materially different methods which have different modes of operation, different functions and different effects. Group II is a living cancer cell line with a mutant

androgen receptor (AR), Group IV is an antiandrogen drug having an antagonistic effect on a mutated AR, Group VI is an antiandrogen drug having no potential to induced a resistant cancer, Group VII is a kit comprising a cell with the AR gene under PSA promoter control for measuring AR transcription, Group X is an isolated protein of SEQ ID NO:2, Group XI is a polynucleotide encoding the protein of SEQ ID NO:2, Group XIII is a compound that alters binding between an androgen and the protein of SEQ ID NO:2, Group XIV is an agent having anti-androgen effect on a mutant AR, Group XVII is an antibody which binds to the protein of SEQ ID NO:2, and Group XX is an agent comprising two or more drugs where each of the drugs has the ability to induce expression of a different AR mutation. The examination of all groups would require different searches in the U.S., international and foreign patent literature and the scientific literature and would require the consideration of different patentability issues. Thus the inventions of Groups II, IV, VI, VII, X, XI, XIII, XIV, XVII and XX are patentably distinct.

7. The methods of Groups I, III, V, VII, IX, XII, XV, XVI, XVIII, IXX, XXI and XXII differ in the method objectives, method steps and parameters, intended populations and in the reagents used. Group I requires a AR+ cancer cell line being induced to mutate the AR under culturing in the presence of an antiandrogen drug in order to observe cell proliferation; Group III requires a mutated AR cell line and an antiandrogen drug and measuring antagonistic effects of the drug in order to select a drug; Group V requires a AR cell line and a antiandrogen drug and measuring cancer cell susceptibility to the drug in order to select a drug having no potential to induced resistance; Group IX

requires a AR+ cell line and an antiandrogen drug and measuring transcriptional activity from the AR gene in order to evaluate the cell for drug responsiveness; Group XII requires a compound, and androgen and a protein of SEQ ID NO:2 and measuring the ability of the compound to change the binding between the androgen and the protein in order to select a compound; Group XV requires a subject having a hormone sensitive cancer and an agent having antiandrogen activity in order to prevent or treat the cancer; Group XVI requires two or more agents having antiandrogen action and a pharmaceutical carrier and combining the components in order to produce a pharmaceutical composition; Group XVIII requires an antibody recognizing the protein of SEQ ID NO:2 and measuring the protein in a sample in order to quantitate the protein; Group IXX requires two or more antiandrogen drugs and an AR+ cell line and culturing the cells in the presence of the different antiandrogens to produce different cell lines having different mutations in the AR in order to classify the antiandrogens on the basis of the AR mutation; Group XXI requires two or more antiandrogen drugs classified on the basis of their ability to induce different AR mutations in a cell line and a subject having a hormone sensitive cancer in order to prevent or treat the cancer; and Group XXII requires a subject having an antiandrogen resistant cancer to an antiandrogen drug and providing a second antiandrogen having the ability to induce a different AR mutation and administering the second drug in order to prevent or treat the hormone sensitive cancer. The examination of all groups would require different searches in the U.S., international and foreign patent literature and the scientific literature and would

require the consideration of different patentability issues. Thus the inventions of Groups I, III, V, VII, IX, XII, XV, XVI, XVIII, IXX, XXI and XXII are patentably distinct.

8. Inventions of Group I and II; Group III and IV; Group V and VI; and Group IXX and XX are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make another and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case the AR-mutant cell line of Group II can be made by recombinant methods such as homologous recombination; the antiandrogen drug of Groups IV and VI can be produced or screened by measuring growth of LNCaP human prostate cancer xenograft; the agent of Group XX can be produced or screened by measuring growth of LNCaP human prostate cancer xenograft and PCR amplification of transcripts to identify mutated AR. The examination of all groups would require different searches in the U.S., international and foreign patent literature and the scientific literature and would require the consideration of different patentability issues. Thus the inventions of Group I and II; Group III and IV; Group V and VI; and Group IXX and XX are patentably distinct.

9. Inventions of Group IV and VII; Group VIII and IX; Group X and XII; Group XIV and XV; Group XIV and XVI; Group XVII and XVIII; Group XX and XXI; and Group XX and XXII are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product

(MPEP § 806.05(h)). In the instant case the method of Group VII can be used with a materially different product such as antibody targeting or any known chemotherapy to target a cancer; the method of Group IX can be used with a materially different product such as a CAT assay; the method of Group XII can be used with a materially different product such as a CAT assay; the method of Group XV can be used a materially different product such as any chemotherapy; the agent of Group XIV can be used in a materially different process such as screening for binding proteins; the antibody of Group XVII can be used in a materially different process such as immunopurifying the protein or in generating anti-idiotypic antibodies; and the methods of Groups XXI and XXII could be practiced with a materially different product such as chemotherapy. The examination of all groups would require different searches in the U.S., international and foreign patent literature and the scientific literature and would require the consideration of different patentability issues. Thus the inventions of Group IV and VII; Group VIII and IX; Group X and XII; Group XIV and XV; Group XIV and XVI; Group XVII and XVIII; Group XX and XXI; and Group XX and XXII are patentably distinct.

10. The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not

commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

11. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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